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Review article

Computer-aided diagnosis: A survey with bibliometric analysis

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ABSTRACT

Computer-aided diagnosis (CAD) has been a promising area of research over the last two decades. However, CAD is a very complicated subject because it involves a number of medicine and engineering-related fields. To develop a research overview of CAD, we conducted a literature survey with bibliometric analysis, which we report here. Our study determined that CAD research has been classified and categorized according to disease type and imaging modality. This classification began with the CAD of mammograms and eventually progressed to that of brain disease. Furthermore, based on our results, we discuss future directions and opportunities for CAD research. First, in contrast to the typical hypothetical approach, the data-driven approach has shown promise. Second, the normalization of the test datasets and an evaluation method is necessary when adopting an algorithm and a system. Third, we discuss opportunities for the co-evolution of CAD research and imaging instruments—for example, the CAD of bones and pancreatic cancer. Fourth, the potential of synergy with CAD and clinical decision support systems is also discussed.

1. Introduction

In the last two decades, significant progress has been made in Information Technology. This includes the proposal of new imaging modalities, because of which developments in the computerized analysis of medical images are expected in the future. Diagnosis through computerized analysis, known as computer-aided diagnosis (CAD), was originally developed for breast cancer using mammography in the 1960s, and has since been extended to the diagnosis of lung cancer, colorectal cancer, and so on [1–3].

Using CAD, doctors, primarily radiologists, can use computer support as a “second opinion” and make a final decision more quickly and with greater confidence. There are two types of CAD research—“Detection” and “Diagnosis”—and it consists of two phases—a “propose phase” and an “evaluation phase” [4] (Fig. 1).

In CAD research, “Detection” implies a technology designed to reduce observational oversight in general by marking the regions of an image that have potential for specific abnormalities. “Diagnosis” implies a technology designed to assess a disease using image-based information. Thus, CAD is an important technology to reduce the burden on doctors and medical staff, and shorten the time required for the interpretation of medical images. Furthermore, CAD systems have increased the accuracy of diagnosis, which has led to their increased use over the years, such that CAD technology is now a major research subject in medicine [1,5–8]. CAD systems might have been separately developed in each department of medicine, such as imaging modalities. However, it is too difficult to comprehensively determine the research trends and the “big picture” in CAD.

In this article, we present an overview of recent developments in CAD to support future cross-sectional studies. In general, there are two main approaches to grasping a research overview: expert-based approach and computer-based approach [9]. The expert-based approach involves convincing, but is often subjective and admits of the possibility that some subjects are overlooked in the research. On the contrary, the computer-based approach presents objective results and provides an accurate overview of the medical scenario in question. Several studies have been conducted using the expert-based approach in CAD [4,6,7,10–15], but these researches have a little chance to overlook the important fact which author did not grasp. Hence, we used a computer-based approach called bibliometric analysis for objective discussion in this paper.

2. Methodology and data

2.1. Methodology

Bibliometrics is a field of research in library and information science (LIS) that features various methods to quantitatively analyze

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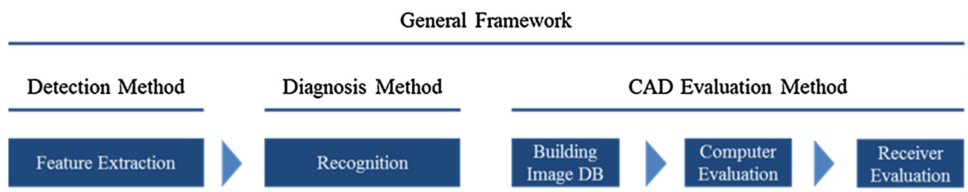

Fig. 1. General CAD framework.

Fig. 2. Methodology overview.

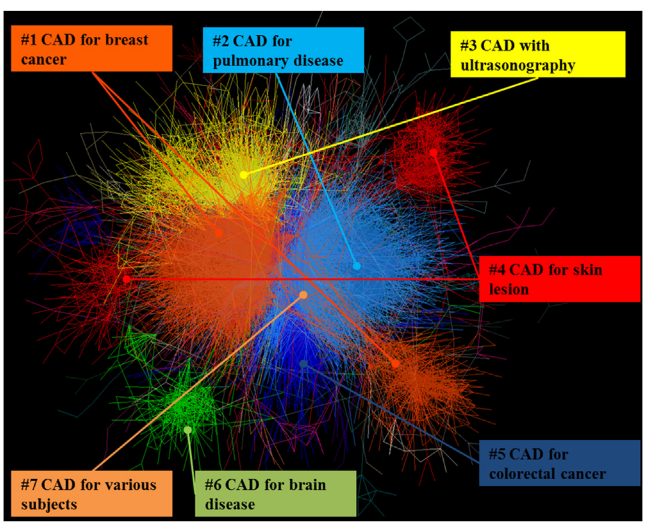

Fig. 3. CAD Academic research overview.

the bibliographic information of papers, patents, and so on. Bibliometric methodologies generally use Information Technology to process and analyze quantitative as well as qualitative data from bibliographic information and provide meaningful implications.

In this research, we selected citation network analysis, which is an effective bibliometrics methodology to identify an overview of an academic field. This technique analyzes the characteristics of a field with little chance of missing important research in each domain [16–19].

Fig. 2 shows an overview of our research methodology [16]. We first acquired relevant CAD research papers from each academic domain of interest using an academic publication database by using selected queries (Fig. 2a). We then constructed a citation network by regarding papers as nodes and direct citations as links (Fig. 2b). We did this because a previous study had indicated that direct citation is the best approach to detect emerging trends [20]. Following this, we eliminated irrelevant papers that were not linked to other papers in the largest graph component of the citation network to focus on the mainstream of research (Fig. 2c). Finally, we organized the network into clusters (Fig. 2d) using a topological clustering method known as Newman's algorithm [21]. In Newman's algorithm, clusters are divided into subsets in accordance with a rule that maximize modularity: Q. Then, Q is defined as follows:

$$Q = \sum_{s=1}^{M} \left[\frac{l_s}{l} - \left(\frac{d_s}{2l} \right)^2 \right], \quad (1)$$

where Q is the independence of a cluster, M is the number of clusters, s is the cluster ID, l is the number of links in the entire network, l_s is the number of links inside module S, and d_s is the total number of links of nodes in S.

Newman's algorithm has been noted to build well-separated clusters in terms of research domains [16–19,22]. The network is visualized using a large graph layout (LGL) [23]. The LGL can help visualize large-scale networks containing thousands of nodes and millions of links within a reasonable computational time. For ease of recognition, intra-cluster links in the same network are expressed in the same color.

Following clustering, we analyzed the characteristics of each cluster, including the average publication year of papers, the number of citations, journal name, and the term frequency-inverse document frequency (tf-idf). Tf-idf is the best approach for discovering corresponding relationships between papers [18], and is defined as follows:

$$\text{Tf-idf} = \frac{n_{i,j}}{\sum_k n_{k,j}} \cdot \log \frac{D}{\{d : d \ni t_i\}}, \quad (2)$$

where t_i is the given term, $n_{i,j}$ is the number of occurrences of term t_i, D is the total number of documents, and d is the number of documents containing term t_i.

In addition to simple keyword analysis; semantic similarities between clusters were measured to investigate semantic linkages of topics in each CAD field [24]. Semantic similarity was measured by cosine similarity [22]; defined as follows;

$$\text{CosineSimilarity}(t, s) = \frac{\bar{j_t} \bullet j_s}{\sqrt{\sum_i j_t^{(i)} \bullet j_s^{(i)}}}, \quad (3)$$

where t and s are clusters in each domain, and j_t and j_s are term vectors of clusters t and s, respectively. Cosine similarity increases when each cluster tends to share the same words more frequently, which implies the existence of common research topics among clusters

2.2. Data

We collected bibliographic data from academic publications related to CAD. Our data, including title, author, publication year,

Table 1
Cluster information summary.

ID	Cluster Info					
	Name	AveragePublication year	# Papers	# Citation	Citation/Paper ratio	Tf-idf
1	CAD for breast cancer	2004.2	1628	10,082	6.2	mammogram breast mass mammography breast cancer
2	CAD for pulmonary disease	2007.0	1345	7805	5.8	nodule lung lung nodule pulmonary pulmonary nodule
3	CAD with ultrasonography	2010.1	652	2275	3.5	breast lesion tumor ultrasound prostate
4	CAD for skin lesion	2009.8	429	1062	2.5	dermoscopy melanoma retinal skin skin lesion
5	CAD for colorectal cancer	2007.7	402	1498	3.7	polyp colonography colonic ctc colonoscopy
6	CAD for brain disease	2011.0	142	400	2.8	alzheimer spect brain pet spect image
7	CAD for various subjects	2009.0	107	132	1.2	osteoporosis bmd liver kidney aih

abstract, address, and references, were retrieved from the Science Citation Index Expanded (SCI-Expanded), the Social Sciences Citation Index (SSCI), the Conference Proceedings Citation Index (CPCI), and the Book Citation Index (BKCI). The information was compiled by Thomson Reuters. We used the Web of Science, a Web-based interface that enables users to access database services. We used the queries "computer-aided diagnosis" and "computer-aided detection," and retrieved 7834 papers published through 2015. The largest graph component contained 5197 papers.

3. Results

3.1. Overview of current CAD research status and trend

Following the clustering of the citation network, CAD research was divided into clusters that depended upon on their direct citation topology. We focused on seven clusters with over 100 papers; an overview of these clusters is provided in Fig. 3 and Table 1. These seven clusters featuring 4705 papers occupied more than 90% of the largest component of the network.

By briefly reviewing the clusters, we determined that CAD-related papers were from the departments of medicine and imaging modalities. We examined the history and progress of CAD by rearranging the clusters according to average publication year (Fig. 4).

Cluster #6 (CAD for brain disease) was the latest, and can be regarded as the popular subject of research in the area in the past few years. On the other hand, cluster #1 (CAD for breast cancer) and cluster #2 (CAD for pulmonary disease) had the highest citation per paper in the seven clusters, which implied significant scientific work in the area and good knowledge sharing in these fields. Cluster #7 (CAD for tooth and internal organs), cluster #4 (CAD for skin lesion), and cluster #6 had lower citations per ratio, and can be regarded as areas with less advanced knowledge sharing where topics of research are quite specific. Moreover, in Fig. 3, cluster #6 has is at a considerable distance from the other clusters, which indicates low inter-citation between it and them.

After reviewing the academic landscape of CAD research, we extracted the top four highest-frequency journals in each cluster (Table 2). The results showed us distinctive features of the major journals (e.g., Society of Photo-optical Instrumentation, Medical Physics, and so on) that were highly cited in each cluster. For example, in cluster #6, journals in computer science (e.g., Lecture Notes in Computer Science, Expert Systems with Applications, and Neurocomputing) were preferred. This may indicate that CAD for brain diseases requires advanced computation methods to process images.

Finally, a heat map analysis was conducted to obtain semantic linkages among the CAD research fields in Fig. 5. Each cell gradient represents relatedness between a pair of clusters: dark blue indicates high relatedness (over 0.1 cosine similarity), light blue indicates low relatedness (under 0.1 cosine similarity), and white implies no relation between the given clusters (cosine similarity is 0). The highest average similarity between clusters was in #1 (0.096) and lowest in #6 (0.014). There was high relatedness between clusters #1 and #3. It is no wonder that #1 had was highly related to #3 because the latter focused on ultrasonography,

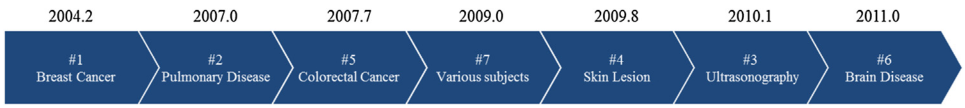

Fig. 4. CAD development history.

Table 2
Journal analysis.

Cluster#	Journal name	Frequency Rate
ALL	P Soc Photo-Opt Ins	7.62%
	Proc SPIE	6.79%
	Med Phys	5.70%
	ACAD Radiol	4.21%
#1	P Soc Photo-Opt Ins	8.60%
	Med Phys	7.19%
	Proc SPIE	5.96%
	Acad Radiol	4.79%
#2	P Soc Photo-Opt Ins	10.41%
	Proc SPIE	7.58%
	Med Phys	7.29%
	Acad Radiol	6.10%
#3	Proc SPIE	8.59%
	Ultrasound Med Biol	6.13%
	Med Phys	5.83%
	P Soc Photo-opt Ins	4.75%
#4	Proc SPIE	5.83%
	IEEE Eng Med Bio	4.90%
	Lect Notes Comput Sc	4.43%
	Skin Res Technol	4.43%
#5	Proc SPIE	11.44%
	P Soc Photo-opt Ins	8.71%
	Med Phys	6.22%
	Acad Radiol	5.72%
#6	Lect Notes Comput Sc	12.68%
	Expert Syst Appl	7.75%
	Neurosci Lett	6.34%
	Neurocomputing	4.93%
#7	Proc SPIE	7.48%
	Med Phys	6.54%
	P Soc Photo-opt Ins	5.61%
	Comput Med Imag Grap	4.67%

	#1	#2	#3	#4	#5	#6	#7	Ave
#1	1.000	0.049	0.385	0.021	0.048	0.012	0.000	0.086
#2	0.049	1.000	0.032	0.025	0.031	0.011	0.032	0.030
#3	0.385	0.032	1.000	0.064	0.038	0.042	0.017	0.096
#4	0.021	0.025	0.064	1.000	0.016	0.000	0.012	0.023
#5	0.048	0.031	0.038	0.016	1.000	0.000	0.018	0.025
#6	0.012	0.011	0.042	0.000	0.000	1.000	0.017	0.014
#7	0.000	0.032	0.017	0.012	0.018	0.017	1.000	0.016

Fig. 5. Heat map analysis.

which modality is mainly intended to diagnose breast tissue and the prostate gland. Hence, it is highly likely that the word "breast" may be regarded as its similarity and relatedness.

There was no relatedness between clusters #4 and #6, clusters #5 and #6, and clusters #1 and #7. This implies that cluster #6 contained methods that were not regarded as standard in clusters #4 and #5, or that there may be opportunities for improvement in cluster #6 by adapting the other clusters' concepts. Further, we concluded that cluster #6, CAD for brain disease, is a highly applied research domain that uses a different technological system from CAD to focus on other regions of the body.

3.2. Overview of sub-fields of CAD research

Following an examination of the overall structure of CAD research, we conducted a survey of each cluster. We selected the top 10 most-cited papers through all years, and also the top 10 most-cited papers published in 2015 from each cluster (thus, a total 20 papers were selected), except for clusters #3 and #7 (we explain the reason for this later), and summarize them in the following. We also measured the basic statistics of each cluster, including the following: summarized author name, publication year, journal name, number of citations in each cluster, main subject, method keyword, and results (Tables 3–10 in the Appendix, Supplementary information).

#1 Breast Cancer CAD (Table 3)

In this cluster, all 20 papers [1,10–12,25–40] were concerned with research on the detection or the diagnosis of breast cancer, and all adopted mammography as imaging modality. Breast cancer CAD can be divided into three topics: "Microcalcifications," "Mass," and "Architectural Distortion" in #1. A large amount of breast cancer CAD research attained the diagnosis phase [10–12,26,28,30,31,35,36,40]. This is why commercial a CAD product (ImageChecker produced by R2 Technology) was produced early on, and research in this area has advanced thoroughly. The maturity of this field was also supported by our analysis, shown in Table 1 and Fig. 4.

#2 Pulmonary Disease CAD (Table 4)

In this cluster, lung nodule detection for pulmonary disease was the main topic, and all 20 papers [2,4,5,13,41–56] adopted CT as imaging modality. To detect lung nodules, two- and three-dimensional analyses are effective [2,44,46]. In contrast to #1, pulmonary disease CAD research can be considered in transition between the development and diagnosis phases.

#3 Ultrasonography CAD (Tables 5 & 6)

In this cluster, treatment pertaining to breast and prostate CAD was expected from the keyword analysis (the top five frequency words were "breast," "lesion," "tumor," "ultrasound," and "prostate"). However, all 20 papers [3,6,14,57–73] focused on breast cancer (Table 5). Therefore, we tried to conduct recursive clustering using the same bibliometric analysis method to extract sub-clusters, and the top 10 cited papers [74–83] are hence listed in Table 6.

In cluster #3 and its sub-clusters, the main modalities were ultrasonography and magnetic resonance (MR) imaging apparatuses, and breast cancer and prostate cancer were studied. As with cluster #1, CAD for breast cancer has developed to the diagnosis phase [3,6,57–60,62–67,69,71], as has CAD for prostate cancer [74,75,77–82].

#4 Skin lesion CAD (Table 7)

In this cluster, the dermoscope was the most verified modality, and skin lesion (especially skin cancer) had been focused on the most [7,15,84–101]. Skin CAD has been used for detection, and some research has used it for diagnosis [86,92,93,97].

#5 Colorectal Cancer CAD (Table 8)

Colonic polyp detection with CT Colonography (CTC) was the focus in this cluster [8,102–120]. Colorectal cancer CAD has not been used for diagnosis, and there were no papers that focused on computer-aided "diagnosis" of the selected ones. Thus, it seems to be in nascent stages of development.

#6 Brain disease CAD (Table 9)

In this cluster, three modalities were discussed [121–140]: Single-photon Emission Computed Tomography (SPECT) [121–124,126,128,130,139], Positron Emission Tomography (PET) [124–126,129], and MR [127,131–138,140]. MR has been the focus in recent research. Alzheimer's disease is the most-cited subject, and machine learning methods, especially support vector machine, were preferred for analysis. The necessity of advanced computing might be the cause of its weak relatedness with other clusters, as shown in Fig. 5.

#7 Various subject diseases CAD (Table 10)

In this cluster, we observed the use of various modalities and a large number of subject diseases in 18 papers [141–158] (this cluster did not have 10 papers published in 2015). For instance, this cluster included osteoporosis on dental panoramic radiographs [142,145,151,154], liver disease [146,149,150,155,156,158], kidney disease [144], and so on. With regard to methodology, auto-segmentation for liver and kidney was considered a popular research domain [144,146,150]. The diversity of modalities and subject diseases might be the cause of weak relatedness with other clusters, as shown in Fig. 5.

4. Discussion

First, as shown in the above results, current CAD research covers a wide range of diseases. In the US, the top 10 causes of death are heart disease (23.53%), cancer (22.52%), respiratory disease (5.74%), accidents (5.02%), stroke (4.97%), Alzheimer's disease (3.26%), diabetes (2.91%), influenza and pneumonia (2.19%), kidney disease (1.81%), and suicide (1.58%) [159]. Within cancer, lung and bronchi, prostate, breast, colon and rectum, and pancreas were the top fatal diseases. To exclude non-disease factors, easy-to-diagnose diseases, and pancreatic cancer, almost all causes of deaths were covered within the major research domain of CAD. Therefore, it can be said that CAD research has developed to meet medical demands.

Second, as shown in Table. 1, clusters #1 and #2 are mature research fields. The research trend has shifted from clusters #1 and #2 to #3-7, whereas research in clusters #1 and #2 is still active, as shown in Fig. 6. In the figure, the solid line shows the sum of the number of papers in each year in clusters #1 (breast cancer CAD) and #2 (pulmonary disease CAD). These two clusters, which are the largest and oldest clusters in our research, contained 2973 papers. On the other hand, the dotted line expresses the same information for clusters #3 (ultrasonography CAD), #4 (skin lesion CAD), #5 (colorectal cancer CAD), #6 (brain disease CAD), and #7 (various subjects). These five clusters contained 1732 papers. The results shown in this figure help us conclude that research relating to typical CAD technology, i.e., breast cancer and pulmonary cancer CAD, peaked early in the first decade of the 21st century; on the other hand, research in other CAD domains has been progressing steadily since.

Third, we showed that papers on Alzheimer's disease were highly cited in the brain disease cluster #6, and had used such statistical methods as principal component analysis (PCA) [122,125,126,135,137,138] and machine learning. For the gold standard of developing a CAD algorithm, engineers conduct feature selection for computer diagnosis with the consultation of doctors, whereas PCA and machine learning, which involve latent variables, can skip this process and deal directly with the medical images. Thus, we can develop a model for CAD using medical image data, even without annotation by doctors. Can we regard this situation as indicating a transition from a hypothetical-testing approach to a data-driven approach? The latter approach may have the potential to show relevant features that even a doctor might not be able to perceive. However, it is difficult to evaluate the quality of a system depending on the data-driven approach. At least, there is little research to evaluate false-negative cases through a medical check and cases where diagnosis by doctor and prediction by machine did not match. Therefore, we need to consider ways to guarantee the outcome in approaches that use latent variables and machine learning. We raise this issue as a common problem to be addressed and resolved in CAD research

Fourth, based on the summary and comparison of the research results (Tables 3–10 in the Appendix, Supplementary information), it is difficult to evaluate the system or algorithm that delivers high performance, or is more effective for diagnosis, because the test datasets and evaluation methods are not standardized. The accuracy of a CAD system not only depends on the algorithm, but also on the quality of the training datasets [160]. The standardization and normalization of datasets and evaluation methods is expected to be quite difficult; however, we need to implement standardization from the perspective of evidence-based medicine. In addition to the necessity of research and evaluation schema for guaranteeing the reliability of methods, a scheme for data collection is necessary to improve performance.

Fifth, we point out the importance of the co-evolution of CAD research and imaging instruments. For the development of CAD research, we need a salient algorithm for modeling as well as medical imaging instruments for measurement. An example is the improvement in MRI accuracy, which will contribute to progress in bone CAD and pancreatic cancer CAD. Bone CAD was not featured in the major research domains that we described. This can be attributed to the fact that computed tomographic scanning is not favored because of radiation exposure; moreover, the bone is not identified clearly with other imaging modalities, such as MRI. Hence, research and development in MRI will improve research in bone CAD. Furthermore, there are cases where early detection is critical for prevention but they are difficult to diagnose early on, such as pancreatic cancer. Pancreatic cancer CAD can be considered a developing research domain in spite of the demand for it [161–165]. This is mainly why it has encountered difficulties in image classification in areas occupied by the pancreatic tumor [162,166]. In developing CAD systems for such cases, it is challenging to collect datasets for early stage detection, let alone from the viewpoint of quality and quantity. Therefore, progress is needed in research on diagnostic imaging instruments for better imaging for some diseases, such as pancreatic cancer CAD.

Finally, in this paper, we only focused on CAD, analyzed its trend, and discussed opportunities through bibliometric analysis in the above. To improve CAD and further develop its contribution to medical treatment, however, we need to expand our research scope from CAD to decision support systems [167–169]. Decision support systems can be regarded as "active knowledge systems which use two or more items of patient data to generate case-specific advice" [170]. For example, in case of the diagnosis of the severity of asthma, it makes use of the patient's symptoms, exacerbations, and spirometry (lung function) as parameters [171]. We illustrate the relationship between CAD and decision support systems for diagnosis in Fig. 7.

Furthermore, we think that CAD systems become much more useful through connectivity with decision support systems, especially for the diagnosis of diseases where the determining factors are various (e.g., Alzheimer's disease (AD) diagnosis). We propose some keys to generate a synergy effect between both technologies in the example of AD diagnosis as follows: First, we need to weigh

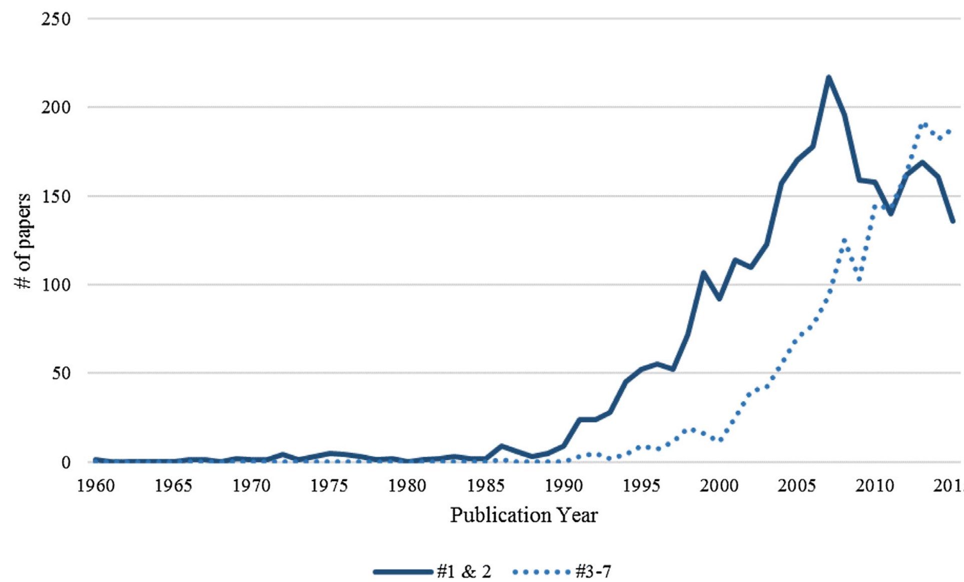

Fig. 6. CAD research trends.

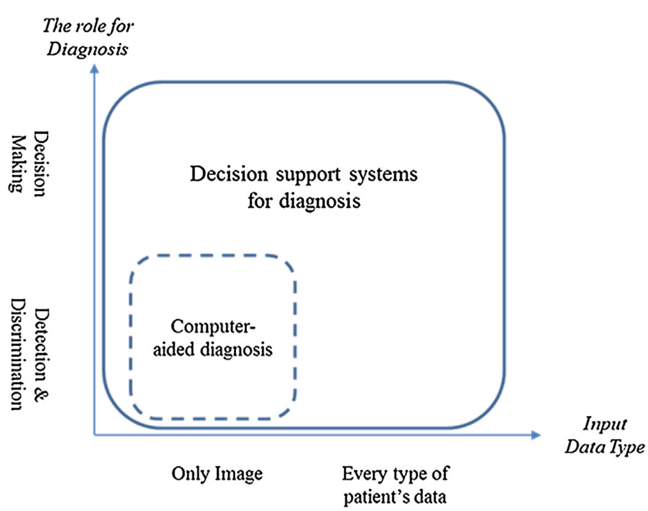

Fig. 7. Relationship between CAD and decision support systems for diagnosis.

Summary points
What was already known

- Computer-aided diagnosis (CAD) has been developed in each medical fields (e.g. gynecology, pulmonary medicine, dermatology)
- It is generally known that the first CAD product is mammograms CAD (ImageChecker produced by R2 Technology), however next generation system has not well-followed.
- So, we do not accurately grasp how to develop CAD research and state-of-the-art technology.

What this study has added

- We showed the CAD research overview and revealed the developmental process and well- noticed technical trend.
- It initially started with mammograms CAD, has progressed to brain disease CAD.
- Our result has synergies and leverages both policymakers and researchers to know research trend on a quantitative basis and to design future research and project on a comprehensive perspective.

each determination factor. In the case of AD, diagnosis is conducted according to the information provided by clinical examination, a thorough interview of the patient and relatives, and medical imaging. The first set of information can be analyzed in decision support systems and the last in CAD systems. Therefore, it is necessary to evaluate each output and integrate all of them. This can make diagnosis more accurate, even in early AD, which is extremely difficult to diagnose at present. Second, we should suppose a comprehensive judgment. There can be a large number of factors to consider for doctors, in addition to medical observation (e.g., patient's quality of life, preference and economic condition, and cost-effectiveness from a social perspective). Ideally, all factors should be analyzed by the decision support systems and CAD should act as a go-between. Third, we need to manage regulations. For practical use of systems, some criteria need to be met to ensure system quality based on the regulations. Therefore, we need to clarify the effects of system output, how each function works with regard to the quality of the system, and why diagnosis results differ in each case. It might be challenging to synchronize CAD with decision support systems.

5. Conclusion

In this paper, we conducted citation network analysis to provide a research-based overview of and trends in computer-aided diagnosis/detection. We determined that CAD research has been classified and categorized by disease type and imaging modality, which began with mammogram CAD, and has since progressed to brain disease CAD. This developmental process is an unprecedented outcome not reflected in any expert-based review paper. A summary of each research domain was also presented, including method and performance. Furthermore, based on the results, we discussed future directions and opportunities for CAD research: the potential for the data-driven approach, the importance of standardizing datasets and evaluation methods, and the expectation of co-evolution of CAD research and imaging instruments. This paper can help policymakers and researchers in radiology, computer vision, and medical imaging by offering a comprehensive picture of CAD research.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijmedinf.2017.02.004.

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